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Atypical Cortical Gyrification in Adolescents with Histories of Heavy Prenatal Alcohol Exposure

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Abstract

Prenatal alcohol exposure can adversely affect brain development, although little is known about the effects of prenatal alcohol exposure on gyrification. Gyrification reflects cortical folding complexity and is a process by which the surface of the brain creates sulci and gyri. Prior studies have shown that prenatal alcohol exposure is associated with reduced gyrification in childhood, but no studies have examined adolescents. Subjects (12–16y) comprised two age-equivalent groups: 30 adolescents with histories of heavy prenatal alcohol exposure (AE) and 19 non-exposed controls (CON). A T1-weighted image was obtained for all participants. Local gyrification index (LGI) was estimated using FreeSurfer. General linear models were used to determine between group differences in LGI controlling for age and sex. Age-by-group interactions were also investigated while controlling for sex. The AE group displayed reduced LGI relative to CON in the bilateral superior parietal region, right postcentral region, and left precentral and lateral occipital regions ($ps < .001$). Significant age-by-group interactions were observed in the right precentral and lateral occipital regions, and in the left pars opercularis and inferior parietal regions ($ps < .01$). The AE group showed age-related reductions in gyrification in all regions whereas the CON group showed increased gyrification with age in the lateral occipital region only. While cross-sectional, the age-related reduction in gyrification observed in the AE group suggests alterations in cortical development throughout adolescence and provides further insight into the pathophysiology and brain maturation of adolescents prenatally exposed to alcohol.

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Keywords

Fetal alcohol spectrum disorders (FASD); Fetal alcohol syndrome (FAS); Prenatal alcohol exposure; Gyrification; Local gyrification index (LGI); structural MRI

1. Introduction

Prenatal alcohol exposure can interfere with embryonic and fetal development and may have long-lasting negative effects. These may include facial dysmorphism, growth retardation, brain alterations, and/or neurobehavioral deficits. Fetal alcohol spectrum disorders (FASD) encompass the range of outcomes that may occur as a result of alcohol consumption during pregnancy.

Neuroimaging studies have furthered our understanding of the effects of prenatal alcohol exposure on brain development. Among the most consistent findings from magnetic resonance imaging (MRI) studies in FASD are reductions in global and regional gray and white matter volumes (for review, see Lebel, Roussotte, & Sowell, 2011). As cortical brain volume is the product of cortical surface area and cortical thickness, two indices that have distinct genetic origins (Panizzon et al., 2009) and developmental trajectories (Raznahan et al., 2011; Wierenga, Langen, Oranje, & Durston, 2014), distinguishing between these two measures of cortical morphology is important. A number of studies have found differences in cortical thickness in individuals prenatally exposed to alcohol compared to non-exposed peers, but these findings have not been consistent. Some studies have reported increased thickness primarily in frontal, parietal, and temporal regions (Fernandez-Jaen et al., 2011; Sowell et al., 2008; Yang et al., 2012), whereas others have found decreased cortical thickness across multiple regions (Robertson et al., 2015; Treit et al., 2014; Zhou et al., 2011). In addition, one study found no differences in cortical thickness between children with alcohol-related neurodevelopmental disorder and typically developing control children (Rajaparakash, Chakravarty, Lerch, & Rovet, 2014). These authors also reported reduced surface area in the right superior temporal gyrus and occipital-temporal region, as well as global surface area reductions in bilateral frontal, temporal, and right occipital cortex that were consistent with overall volumetric reductions of these areas. In a more recent study, we found that adolescents with heavy prenatal alcohol exposure had reduced surface area of the anterior cingulate cortex compared to non-exposed adolescents (Migliorini et al., 2015). Given the known reductions in cortical volume and the discrepant findings concerning cortical thickness, examining additional morphological features will lead to a greater understanding of structural brain alterations in individuals with heavy prenatal alcohol exposure.

One important morphological feature of the cerebral cortex is gyrification or the degree of cortical folding. Gyrification is a process by which the surface of the brain undergoes changes to create sulci and gyri. This neuroanatomical folding enables an expanded cortex to fit within the cranium while promoting efficiency of neuronal connections (White, Su, Schmidt, Kao, & Sapiro, 2010). Cortical folding begins during gestation, with considerable folding occurring during the third trimester (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995; Dubois et al., 2008). Since the vast majority of cortical folding occurs during fetal

brain development, this morphological feature may be particularly susceptible to environmental insults, such as prenatal exposure to alcohol.

Although more research is needed to determine the relation between cognitive abilities and gyrification, a recent study in healthy adults found that greater cortical gyrification (particularly in the lateral frontal cortex) was associated with greater performance in tasks of executive functioning (Gautam, Anstey, Wen, Sachdev, & Cherbuin, 2015). Another study found that regional increases in gyrification were associated with higher general intelligence scores in healthy subjects (Luders et al., 2008) and reduced gyrification has been found among individuals with intellectual disability (Zhang et al., 2010). Lower IQ and executive functioning deficits have been consistently reported among individuals with FASD (for review, see Mattson, Crocker, & Nguyen, 2011). Understanding the impact that prenatal alcohol exposure has on gyrification might provide further insight into the cognitive and behavioral deficits associated with FASD.

The Gyrification Index (GI), a ratio of the inner and outer cortical contour of the brain (Zilles, Armstrong, Schleicher, & Kretschmann, 1988), is a widely used method to quantify cortical folding. While informative, the GI method has some limitations (Schaer et al., 2008). For example, the GI is a global measure that does not provide any region-specific information, and its calculations are based on 2-dimensional measurements that do not account for the 3-dimensional nature of the cerebral cortex. The local gyrification index (LGI), an extension of the GI metric, is a more recently developed surface-based automated 3-dimensional approach that quantifies the amount of cortex buried with the sulcal fold compared to the amount of visible cortex in a circular region of interest (Schaer, et al., 2008). To our knowledge, no study has used this approach to examine differences in cortical folding across the entire brain in individuals with FASD compared to non-exposed peers.

A recent study by De Guio et al. (2014) examined cortical folding in 9 year-old children with FASD using global and regional sulcal indices (i.e., the ratio between the area of the sulcus and the outer cortical area), a method slightly different than the standard GI. Findings revealed that reduced global cortical folding corresponded with increasing levels of alcohol exposure in children with FASD. However, the impact of prenatal alcohol exposure on gyrification in adolescents has yet to be explored. In healthy individuals, gyrification is thought to decrease with age during this period. For example, in a cross-sectional study Klein et al. (2014) examined the influence of age on cortical folding patterns in subjects aged 12 to 23 years and found reduced gyrification with increasing age in several regions. A longitudinal study examining changes in gyrification across ages 6 to 30 years found that most regions showed no change or a linear decrease with age (Mutlu et al., 2013). Another longitudinal study found that in healthy individuals, gyrification across the brain follows a cubic trajectory with overall reductions occurring across 8–22 years of age (Raznahan et al., 2011).

In the current cross-sectional study, we used a whole-brain surface-based approach to examine the degree of gyrification in adolescents with heavy prenatal alcohol exposure and demographically-similar non-exposed controls. The use of a surface-based approach was preferred because it provides more precise measurements of the cerebral cortex, identifying

subtle alterations that may not be captured using volume-based approaches. In addition, evidence has shown that the effects of prenatal alcohol exposure on brain development are not uniform across all brain regions. Comparing LGI at each vertex across the whole brain allowed us to detect specific areas that differed most between groups. Based on previous findings of global reductions in cortical folding (De Guio et al., 2014), we hypothesized that alcohol-exposed adolescents would display widespread local gyrification reductions. Further, given previous findings of altered developmental trajectories of cortical volume in children and youth with heavy prenatal alcohol exposure (Lebel, et al., 2012) we hypothesized that alcohol-exposed adolescents would show a steeper decline in gyrification with age. Overall, understanding the impact of prenatal alcohol exposure on cortical folding will expand our knowledge of brain abnormalities in FASD and help elucidate complex structural changes that may underlie the cognitive and behavioral deficits often reported in this population.

2. Results

2.1 Subject characteristics

The AE and CON groups did not differ on sex [$\chi^2(df=1) = .15, p = .703$], race [$\chi^2(df=2) = .12, p = .943$], ethnicity [$\chi^2(df=1) = .13, p = .715$], handedness [$\chi^2(df=2) = 1.76, p = .415$], SES [$F(1, 47) = 1.27, p = .266$], or age [$F(1, 47) = .29, p = .591$]. As expected, adolescents in the AE group had significantly lower FSIQ scores than adolescents in the CON group, $F(1, 47) = 15.72, p < .001$. No significant between group differences were observed for TIV $F(1, 47) = 2.525, p = .119$. Descriptive characteristics of the AE and CON subjects are presented in Table 1.

2.2 Between group analyses

After controlling for sex and age, adolescents in the AE group showed significant LGI reductions compared to adolescents in the CON group in five clusters (all $ps < .001$) (Figure 1, clusters 1–5). Two clusters were found in the right hemisphere. The peak vertex for cluster 1 was located within the superior parietal gyrus with the cluster covering portions of the cuneus, precuneus, medial lingual gyrus, and lateral occipital cortex. Cluster 2 had its peak vertex within the postcentral gyrus but also covered portions of the precentral gyrus, insula, and pars opercularis. Three left hemisphere clusters were identified. For cluster 3, the peak vertex was located within the precentral gyrus. This large cluster included portions of the postcentral gyrus, pars opercularis, insula, and the medial temporal gyrus. Cluster 4 had a peak vertex within the superior parietal cortex and also included portions of the postcentral gyrus. Finally, the peak vertex for cluster 5 was located within the lateral occipital cortex and the cluster additionally covered portions of the superior parietal and inferior temporal gyri. Coordinates for the peak vertices of these clusters and additional cluster characteristics are presented in Table 2.

2.3 Age-by-Group interaction analyses

After controlling for the effects of sex, significant group differences in the age-by-gyrification correlations were observed in both hemispheres (all $ps < .01$) (Figure 2a, clusters 6–9). Within the right hemisphere, cluster 6's peak vertex was within the precentral

gyrus. This cluster also included portions of the superior frontal gyrus. Cluster 7 had peak coordinates in the lateral occipital gyrus and also included portions of the superior and inferior parietal gyri and precuneus. Within the left hemisphere, cluster 8 had a peak vertex located within the pars opercularis. This cluster also covered portions of the rostral middle frontal gyrus. Cluster 9's peak was found within the inferior parietal gyrus. This cluster also covered portions of the banks of the superior temporal sulcus. Coordinates for the peak vertices of these clusters and additional cluster characteristics are presented in Table 3. Post hoc Pearson correlations between age and the mean LGI extracted from each significant cluster were run within each group separately. We found that subjects in the AE group showed a negative correlation between age and gyrification in each of the four clusters (cluster 6: $r = -.599$, $p < .001$; cluster 7: $r = -.524$, $p = .003$; cluster 8: $r = -.417$, $p = .022$; cluster 9: $r = -.379$, $p = .039$). In the CON group, a positive correlation between age and LGI was found in only one cluster, with peak coordinates in the right lateral occipital gyrus ($r = .505$, $p = .027$). Scatterplots illustrating these relationships are shown in Figure 2b.

3. Discussion

We used a 3-dimensional surface-based technique to measure local changes in gyrification (LGI) in adolescents with heavy prenatal alcohol exposure. Specifically, when controlling for age and sex effects, reduced gyrification was observed in alcohol-exposed adolescents in comparisons to demographically similarly non-exposed controls in several cortical clusters. These were located mainly in bilateral parietal and lateral occipital cortices, and the left inferior frontal, insular, and temporal cortex. In addition, we found that in alcohol-exposed adolescents gyrification decreased with age in clusters within the right frontal and occipital cortices as well as in the left frontal and parietal cortices.

Reduced gyrification in alcohol-exposed individuals has been observed in previous investigations. For instance, in a recent report by De Guio et al. (2014), the authors found decreased cortical folding in a group of 9-year alcohol-exposed children. However, it is important to note that in the study by De Guio et al. (2014) used a region of interest approach and measured the degree of gyrification using global and regional sulcal indices. Our study did not use the same methodological approach but rather used a more exploratory technique to examine gyrification at thousands of points over the entire cortical surface. Atypical gyrification has also been noted in case studies, which documented polymicrogyria in individuals prenatally exposed to alcohol (Clarren, Alvord, Sumi, Streissguth, & Smith, 1978; Peiffer, Majewski, Fischbach, Bierich, & Volk, 1979; Reinhardt, Mohr, Gartner, Spohr, & Brockmann, 2010).

The trajectory of cortical development is altered in alcohol-exposed individuals. For example, in a longitudinal study alcohol-exposed children and adolescents displayed a more linear decline of cortical volume over time rather than the expected inverted U-shaped pattern observed in more typical development (Lebel, et al., 2012). Our study suggests that a change in the developmental trajectory of gyrification may also occur, though this has not yet been tested longitudinally. The expected annual change in gyrification is relatively small, with the largest changes occurring prior to age 12 (Raznahan, et al., 2011). We did not observe a decline in gyrification across age in controls. As our sample of adolescents

were aged 12–16 years we may have missed the opportunity to detect the majority of age-related effects in our controls. However, if alcohol-exposed individuals have a late-onset developmental trajectory our finding of a more rapid decline in gyrification during adolescence may be related to delayed brain maturation.

Atypical gyrification has been found in a number of disorders, including velocardiofacial syndrome (Schaer et al., 2009), Williams syndrome (Schmitt et al., 2002), autism (Wallace et al., 2013), schizophrenia (Palaniyappan & Liddle, 2012), and attention-deficit/hyperactivity disorder (ADHD; Wolosin, Richardson, Hennessey, Denckla, & Mostofsky, 2009), among others. One important consideration is that in our sample of alcohol exposed children 76.67% met criteria for an ADHD diagnosis. Therefore, it is possible that the atypical gyrification we observed could be attributed to other diagnoses, such as ADHD, rather than prenatal alcohol exposure. However, while children with idiopathic ADHD may have delayed trajectories for cortical thickness and surface area, these children do not show differences in the gyrification trajectory (Shaw et al., 2012). We found that adolescents with histories of heavy prenatal alcohol exposure, on the other hand, displayed both decreases in gyrification and evidence of a more rapid decline of gyrification. Thus, while the majority of children with prenatal alcohol exposure in our study had ADHD, the observed difference in cortical gyrification between alcohol-exposed children and controls is not likely explained solely by the presence of ADHD. Direct comparisons of cortical folding between children with prenatal alcohol exposure and non-exposed children with ADHD are an important comparison and will be addressed in future studies.

Prenatal exposure to alcohol may differentially impact distinct morphological features of the cortex, including thickness, surface and gyrification. Our findings highlight the presence of alterations in cortical morphology in adolescents with heavy prenatal alcohol exposure. Because cortical folding is known to influence surface area, and cortical volume is the product of surface area and thickness, regions of reduced gyrification may contribute to consistently reported brain volumetric reductions in individuals prenatally exposed to alcohol. We found reduced gyrification in clusters within the lateral occipital, frontal and temporal cortices. Surface area reductions in children with alcohol-related neurodevelopmental disorder have been previously found in similar regions (Rajaprakash et al., 2014). Although additional research examining cortical folding patterns in individuals with FASD is needed, we can speculate that the location of the regions in which the AE group showed reduced gyrification compared to the CON may contribute to some of the cognitive and behavioral deficits often found in this population. For example, decreased gyrification in the superior parietal cortex may represent a neural substrate for working memory deficits in alcohol-exposed individuals, as this region plays a critical role in this domain (Koenigs, Barbey, Postle, & Grafman, 2009). Future studies should examine the relationship between gyrification and cognitive function in individuals with prenatal exposure to alcohol.

3.1 Limitations

Our sample size is relatively small, which precluded examination of the effects of sex. We included sex in our model to account for such differences but were unable to draw any

meaningful conclusions regarding possible interactions of sex and group because we were statistically underpowered for this comparison. An additional limitation to the current study is that the use of psychiatric medication differed between groups. Thirteen children in the AE group were on routinely prescribed psychiatric medication at the time of their scanning appointment. Research has shown that these medications can alter brain structure, but the overall impact of such treatment appears to be ameliorative (Singh & Chang, 2012). Thus, the inclusion of alcohol-exposed subjects with histories of psychiatric medication treatment may actually result in a more conservative estimate of gyrification differences between the groups, assuming the medication results in ‘normalization’ of cortical fold structure (Singh & Chang, 2012). Another limitation is the study’s cross-sectional design; therefore findings of age related changes in LGI should be interpreted with caution. Longitudinal studies with multiple time points and larger sample sizes are necessary in order to gain a better understanding of alcohol’s effect on brain developmental trajectories.

3.2 Conclusions

Altered gyrification during adolescence, a critical period of brain development, may reflect changes in underlying brain connectivity. The age-related reduction in gyrification observed in adolescents with prenatal alcohol exposure suggests alterations in cortical development throughout this period. This finding is consistent with recent longitudinal work describing an atypically linear pattern of cortical volume reduction over childhood and adolescence (Lebel et al., 2012). Our study provides further insight into the pathophysiology and brain maturation of individuals prenatally exposed to alcohol. Identifying the brain mechanism of cognitive dysfunction in FASD can serve to inform and improve treatment of these deficits.

4. Experimental procedure

Thirty adolescents aged 12 to 16 with histories of heavy prenatal alcohol exposure (AE group) and 19 non-exposed controls (CON group) were included in this study. As part of this larger study, Full Scale IQ (FSIQ) scores, from the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) (Wechsler, 2003), and socioeconomic status, measured by the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975), were available for all participants. Written informed parental consent and subject assent were obtained prior to participation. The Institutional Review Boards of San Diego State University (SDSU) and the University of California San Diego (UCSD) approved all study procedures. Subjects received a financial incentive for participating in the study.

4.1 Subjects

All subjects were recruited as part of a larger ongoing study on the behavioral teratogenicity of alcohol at SDSU. Adolescents in the AE group were recruited into this larger study via professional or self-referral. Non-exposed adolescents were recruited from the community via advertising at various agencies and child-related venues. In all cases, multiple sources of information, including medical, social, and/or adoption agency records, and maternal report when available, were used to determine prenatal exposure to alcohol and other teratogens. Study participants were evaluated for fetal alcohol syndrome (FAS) by a pediatric dysmorphologist with expertise in alcohol teratogenesis. Diagnosis was based on the

presence of craniofacial abnormalities requiring at least two of the following: short palpebral fissures, smooth philtrum, thin vermillion; evidence of prenatal and or postnatal growth retardation (height or weight ≤ 10 percentile); and evidence of deficient brain growth or abnormal morphogenesis including at least one of the following: structural brain abnormalities or head circumference $\leq 10^{\text{th}}$ percentile (Hoyme et al., 2005). Nine subjects met criteria for a diagnosis of FAS. A diagnosis of FAS was sufficient but not necessary to meet study criteria for inclusion in the AE group, if alcohol exposure was known or suspected. For those who did not meet criteria for a diagnosis of FAS, documented history of heavy prenatal alcohol exposure was required. As the majority of adolescents in the AE group no longer resided with their biological families, direct maternal report was available for only two children in the AE group. For these cases heavy alcohol exposure was defined as maternal consumption of ≥ 4 drinks per occasion at least once per week or ≥ 14 drinks per week several times during pregnancy. For the remaining subjects in the AE group, mothers were reported to be “alcoholic” or have had alcohol abuse or dependence during pregnancy. The majority of subjects in the CON group resided with their biological mothers, thus screening for exposure to alcohol or other teratogens was typically determined through direct maternal report. Adolescents in the CON group had no exposure or minimal exposure to alcohol prenatally, defined as an average of ≤ 1 drink per week and never more than 2 drinks on a single occasion during pregnancy. Maternal report was not available for two participants in the CON group. For these cases, a record review confirmed absent or minimal prenatal alcohol exposure. These procedures are in agreement with normative standards for retrospective confirmation of maternal alcohol use within the field of clinical behavioral teratology (Mattson et al., 2010).

Exclusion criteria for both study groups were as follows: history of head trauma or loss of consciousness >30 min, MRI contradictions (e.g., metallic implants), non-fluent English speaker, or a medical condition preventing participation. In addition, primary caregivers completed the clinician-assisted National Institute of Mental Health Diagnostic Interview Schedule for Children (C-DISC-4.0; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) to assess for the presence of Axis I psychiatric disorders. Given the increased rate of psychiatric disorders in youth with heavy prenatal alcohol exposure, particularly ADHD (Fryer et al., 2007), excluding those who meet Axis I psychiatric diagnoses would result in a non-representative sample. Twenty-nine subjects (96.7%) in the AE group met criteria for an Axis I disorder, including 23 (76.7%) who met criteria for an ADHD diagnosis. One subject (5.3%) in the CON group met criteria for an AXIS I disorder (specific phobia).

4.2 Image acquisition

All subjects were scanned at the UCSD Center for Functional MRI. Structural imaging was performed on a 3-Tesla CXX4 short bore Excite-2 MR system (General Electric, Milwaukee, WI) with an 8-channel head gradient coil. A high-resolution T1-weighted anatomical scan (fast spoiled gradient sequence, TR = 8000 ms, TE = 3.1 ms, flip angle = 12° , matrix size = 256×192 mm, field of view = 24 cm, slice thickness = 1 mm, acquisition time = 7 min, 24 s) was acquired for each participant. The anatomical scan was collected as part of a larger imaging battery, which included two functional MRI tasks not presented

here. To reduce head motion, foam cushions were placed between the participant's head and the head coil. Subjects watched a movie during the anatomical scan.

4.3 Image processing

Anatomical reconstruction of cortical surfaces from the T1-weighted MRI was performed using the FreeSurfer (v5.3) software package. Briefly, this automated process includes: Talairach transformation, motion correction, intensity normalization, skull stripping, segmentation and tessellation of the gray and white matter boundary, inflation of folded surface tessellation, and automatic topology correction. This method has been previously described in detail (Dale, Fischl, & Sereno, 1999; Fischl, Liu, & Dale, 2001; Fischl et al., 2002). Reconstructed images were visually inspected for significant subject motion and accuracy of the autonomously generated boundaries. In two subjects (1 AE; 1 CON), manual editing was performed to correct for local defects of the pial surface. Two subjects (1 AE; 1 CON), not described in this sample, were excluded from analyses due to excessive motion artifact. Following cortical reconstruction, automated cortical parcellation was conducted according to the Desikan-Killiany atlas (Desikan et al., 2006).

4.3.1 Local gyrification index—The local gyrification index (LGI) is a validated metric built-in to FreeSurfer software (Schaer, et al., 2008) to quantify the degree of cortical folding. The estimated LGI is a vertex-wise extension of the classical two-dimensional GI proposed by Zilles et al. (1988), which is measured as a ratio of the total pial surface and outer cortical contour of the brain. In contrast, the LGI is calculated for each vertex of the cortical surface of each participant as the ratio of the pial surface area to the outer surface of a three-dimensional circular region of interest centered at this vertex (as described in Schaer, et al., 2008). After all anatomical images were processed, each subject was resampled into a common template and the LGI was calculated on the mesh representation of the pial surface. Gyrification maps were generated from the pial surface of each brain where each vertex represented the amount of cortex buried within the sulcal folds. Values (1–5) were assigned to each vertex and its surrounding circular region. Higher values represent greater gyrification whereas an index of 1 indicates a flat cortical surface. The advantage to LGI is that it reports gyrification differences on a regional scale rather than a global scale, thereby providing a more robust measure of gyrification differences between groups.

4.4 Statistical analyses

Subject characteristics were analyzed using chi-square (sex, race, and handedness) or standard analysis of variance (ANOVA) techniques [age, full scale IQ (FSIQ), and socioeconomic status (SES; Hollingshead, 1975) with SPSS 21.0 (IBM Corporation, 2012). Given the theoretical relationship between age, sex and structural brain variables these were included as covariates. While FSIQ may be related to cortical folding, diminished intellectual capacity is consistently reported in individuals with heavy prenatal alcohol exposure (for review, see Mattson et al., 2011). Thus, FSIQ was not included as a covariate in these analyses because statistically controlling for a variable on which populations differ would violate ANCOVA assumptions. Failure to meet these assumptions could produce overcorrected, anomalous, and counterintuitive findings (Dennis et al., 2009).

Whole-brain group comparisons of gyrification used a template surface (fsaverage) provided with FreeSurfer. As the cortical LGI maps are already relatively smooth (Schaer et al., 2012), no additional smoothing was applied to the data prior to group analyses. Statistical analyses were implemented using a general linear model (GLM) with the Query Design Estimate Contrast (QDEC) interface of FreeSurfer. The GLM was estimated at each vertex across the outer surface, with LGI as the dependent variable. GLMs were run for each hemisphere separately. First, we examined group differences in LGI controlling for sex and age. Additional GLMs (conducted separately for each hemisphere) were performed to examine if the relation between age and gyrification differ by group (age-by-group interaction). To set up a group by age interaction we defined group as the independent variable (coded as 0 and 1) and age as a continuous covariate; the product of group and age comprised the interaction term. Nonessential multicollinearity was reduced by mean centering age. The age-by-group interaction was examined using the different onset, different slope (DODS) option in QDEC, which automatically creates the design matrix. For each GLM, results were visualized by overlaying significant clusters onto the inflated cortical surface. All results were corrected for multiple comparisons using a Monte Carlo simulation procedure, implemented in QDEC (Hagler, Saygin, & Sereno, 2006), with a cluster-wise threshold of $p < .05$. The mean LGI was extracted from clusters showing a significant age-by-group interaction for follow-up. Within group Pearson correlation analyses were used to determine the strength of the linear relation between age and mean LGI for each significant cluster.

Findings from a recent study suggest that in children with FAS related microcephaly, gyrification indices (folding intensity and pattern) could be predicted by the degree of brain volume reduction (Germanaud et al., 2014). To ensure that brain volume did not impact our results, all analyses were repeated with the addition of total intracranial volume (TIV; calculated within FreeSurfer) as a covariate. However, there were no relevant changes in our results following the inclusion of TIV (data not shown).

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Figure 1. Inflated cortical curvature maps showing clusters (corrected for multiple comparisons, $p < .05$) of significant reduced gyrification in adolescents with heavy prenatal alcohol exposure relative to controls. The cluster numbers correspond to those described in Table 2.

Figure 2.

Figure 2a. Inflated cortical curvature maps showing clusters (corrected for multiple comparisons, $p < .05$) of significant group differences in the association between gyrification and age. The cluster numbers correspond to those described in Table 3.

Figure 2b. Scatterplots for clusters showing significant group differences in the association between gyrification and age.

Table 1

Demographic Information.

Variable	AE (<i>n</i> =30)	CON (<i>n</i> =19)
Sex (% male)	63.33	57.89
Ethnicity (% Non-Hispanic)	63.33	68.42
Race (% White)	63.33	63.16
Handedness (% Right)	83.33	94.74
Age in years [<i>M</i> (<i>SD</i>)]	14.94 (1.21)	15.14 (1.42)
SES [<i>M</i> (<i>SD</i>)]	45.23 (12.21)	49.45 (13.64)
FSIQ [<i>M</i> (<i>SD</i>)]*	86.90 (14.68)	103.21 (12.91)

*
p < .001

Table 2

Clusters (corrected for multiple comparisons, $p < .05$) demonstrating group differences in gyrification controlling for age and sex.

Cluster	Cluster Number	Size (mm ²)	Peak Vertex MNI coordinates (x, y, z)	Clusterwise p -value	Number of vertices
R superior parietal	1	8248.68	15.5, -35.1, 66.9	0.0001	15863
R postcentral	2	1509.33	48.9, -10.5, 16.4	0.0001	3561
L precentral	3	7643.66	-57.2, 4.2, 8.7	0.0001	17630
L superior parietal	4	1990.97	-32.0, -50.3, 59.2	0.0001	4662
L lateral occipital	5	5473.44	-6.2, -95.6, 12.8	0.0001	7628

Note. R=Right; L=Left

Table 3

Clusters (corrected for multiple comparisons, $p < .05$) demonstrating an age-by-group interaction in gyriification after controlling for sex.

Cluster	Cluster number	Size (mm ²)	Peak Vertex MNI coordinates (x, y, z)	Clusterwise p -value	Number of vertices
R Precentral	6	1882.54	21.7, -6.9, 49.3	0.0001	4249
R Lateraloccipital	7	4162.47	47.4, -70.1, 9.3	0.0001	7560
L Parsopercularis	8	729.27	-53.0, 15.7, 13.6	0.0017	1313
L inferiorparietal	9	614.93	-44.9, -55.9, 13.0	0.006	1284

Note. R=Right; L=Left.